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Lack of eukaryotic initiation factor 3f expression promotes disuse atrophy in mouse skeletal muscle

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**INTRODUCTION**

Muscle mass homeostasis is controlled by protein synthesis and degradation. The eukaryotic initiation factor 3f, a subunit of the eukaryotic initiation complex of translation eIF3, plays an important role in the atrophy/hypertrophy antagonism. eIF3f is a fundamental element of MTORC1 pathway, allowing the physical interaction between S6K1 and MTOR. While homozygous eIF3f knockout showed embryonic lethality, heterozygous knockout mice generated in our laboratory were viable and fertile. The aim of this study was to investigate in vivo the influence of eIF3f expression during skeletal muscle disuse. Wild-type and eIF3f+/− mice were subjected to hindlimb immobilization. Analysis of mass variations, cross-sectional areas, synthesis flows, S6K1 activity and eIF3f expression were conducted on quadsiceps muscles.

**MATERIAL & METHODS**

6-9-months-old C57BL/6 WT and eIF3f−/− males mice were submitted to unilateral immobilization for 3, 7 or 14 days. Mice were anesthetized by isoflurane inhalation to gently fix adhesive bandage. Opposed hindlimb was used as an internal control. A puromycin injection (0.04 µmol/g) was performed 15 minutes before cervical dislocation.

**RESULTS**

Larger decrease of muscle mass in eIF3f−/− mice during immobilization.

69.9% ± 4.3% of muscle mass was lost in eIF3f−/− mice during immobilization compared to the WT group (91 ± 24% of muscle mass).

eIF3f−/− mice show faster and larger CSA reduction of quadsiceps myofibers during immobilization.

Reduced CSA of muscle fibers were observed in eIF3f−/− mice during immobilization.

eIF3f expression level in eIF3f−/− mice is 50 % lower in non-immobilized hindlimb and shows larger decrease during immobilization.

Lack of eIF3f expression results in a stronger decrease in muscle CSA during immobilization.

Less activity of S6K1 in eIF3f−/− mice during immobilization.

In the eIF3f−/− mice, S6K1 activity was significantly lower during immobilization compared to the WT group.

Reduced eIF3f expression level exacerbates protein synthesis reduction during immobilization.

Puromycin incorporation was lower in eIF3f−/− mice during immobilization.

**CONCLUSION**

Unilateral immobilization negatively impacts muscle mass, cross-sectional area of myofibers, rate of protein synthesis with an increase of MTOR activity. Activation of MTOR helps to alleviate the atrophic effect of muscle disuse. The reduction of eIF3f expression level in heterozygous mice results in a stronger atrophy, with a larger decrease in muscle mass and protein synthesis associated to a reduced MTOR activation. These results confirm in vivo the essential role of eIF3f in muscle mass homeostasis.